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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,966	07/28/2003	Laura P. Hale	1579-852	2269

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,966	HALE, LAURA P.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/20/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *4 and 8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election

1. Applicant's election with traverse of Group I, claims 1-8, and the species polypeptide, *in vivo*, and topically in the reply filed on June 20, 2006 to the Office Action of June 12, 2006 is acknowledged and entered. The traversal to Groups I and II and the species elections, particularly species group C, is on the ground(s) that no undue burden would be placed on the Examiner if all of the claims and species were examined.

This is not found persuasive because the inventions are classified in separate classes. Thus, each invention has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. This would necessitate different searches in the patent and or non-patent literature and the consideration of different patentability issues. Furthermore, although the elected species are related, they are patentably distinct and would require different searches. The literature search, particularly relevant in this art, is not coextensive. For example, the method involving the use of zinc alpha-2-glycoprotein (ZAG) nucleic acid relates to gene therapy, which would require independent searching from that required for the method using ZAG protein. Additionally, treatment with ZAG topically versus systemically requires the searching of different method steps and the searching for information supporting the effectiveness of these different modes of treatments. Thus, different searches and issues are involved in the examination of each species.

For these reasons, the restriction requirement is deemed to be proper and is therefore made FINAL.

2. Claims 1-11 are pending.

3. Claims 4 and 8-11 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-3 and 5-7 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting melanin synthesis comprising contacting melanocytes *in vitro* with an amount of ZAG sufficient to effect said inhibition, does not reasonably provide enablement for a method of inhibiting melanin synthesis comprising contacting melanocytes *in vivo* with an amount of ZAG sufficient to effect said inhibition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting melanin synthesis *in vivo* comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition. The claims encompass contacting any melanocyte in any location with an amount of ZAG sufficient to effect inhibition of melanin synthesis.

The specification teaches that ZAG is a plasma glycoprotein that was named for its electrophoretic mobility and for its ability to be precipitated by Zn. Furthermore the specification teaches that ZAG has been detected immunohistochemically in normal secretory epithelial cells of breast, prostate, and liver, in salivary, bronchial, gastrointestinal, and sweat glands and in normal stratified epithelia including epidermis, p. 1 lines 10-18.

The specification teaches that consistent with ZAG's production by secretory epithelium, ZAG is present in most body secretions and constitutes 2.5% and 30% of the proteins present in saliva and seminal fluid, respectively, p. 1, lines 19-21.

The specification teaches that ZAG is produced by normal epidermal keratinocytes, where its expression increases with cellular differentiation. The specification further teaches that keratinocyte-derived factors influence melanocyte behavior, including melanocyte proliferation, dendricity, and total melanin production, p. 7, lines 5-9. The specification also teaches that ZAG has been identified in epidermal malignancies including squamous, Merkel cell, and basal cell carcinomas, p. 2, lines 5-7.

The specification teaches that moderate to high levels of ZAG are required to achieve significant inhibition of melanin synthesis and that B16 cells are normally highly melanized despite their production of low levels of murine ZAG, para. bridging p. 7 and 8. Further the specification teaches that a threshold amount of ZAG may be required for simultaneously

decreasing both melanogenesis and melanin secretion, p. 8, lines 9-11. The specification teaches that B16 melanoma cells that are either transfected to strongly express ZAG or treated with exogenous ZAG have decreased melanin production *in vitro*, p. 7 lines 13-15 and Figs. 1-3. ZAG transfected B16 tumors constitutively expressing ZAG also have decreased growth and form amelanotic tumors *in vivo*, p. 7, lines 15-16. Purified ZAG, the specification teaches, also decreased melanin production by B16-V cells *in vitro*, p. 7, lines 19-20. Further the specification teaches that constitutive expression of ZAG appears to decrease ZAG transfected tumor cell line melanin synthesis in the transfected cells *in vivo* more strongly relative to its effects *in vitro*, indicating that ZAG may also act through other indirect mechanisms *in vivo*, p. 7, lines 22-25 and Figs. 1-4.

The specification hypothesizes that the observation that ZAG-transfected tumor cells that make melanin *in vitro* are amelanotic *in vivo* demonstrates that the concentration of ZAG required to inhibit melanin synthesis is readily achieved at tumor sites *in vivo*, p. 8, lines 11-14 and Fig. 4B. Furthermore, the specification teaches that ZAG similarly decreases melanin production in primary murine melanocytes *in vitro*, p. 7, lines 25-26 and Fig. 5.

One cannot extrapolate the teachings of the specification to the scope of the claims because (1) it is well known in the art that *in vitro* cultured cells have different characteristics than cells in the *in vivo* host animal and, additionally, (2) one cannot predict without undue experimentation the amount of ZAG sufficient to inhibit melanin synthesis by topical administration of ZAG *in vivo* given the known presence in the art of ZAG in the epidermis and in sweat which contacts the epidermis.

In particular, regarding the effects of ZAG *in vitro* on cultured cells, the differences between cells in culture and primary cancer cells are well known in the art. In particular, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*).

Furthermore, regarding the studies with B16 melanoma cells, either endogenously expressing ZAG or constitutively overexpressing human ZAG, Dermer teaches (Bio/Technology, 1994, 12:320) that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Those of skill in the

art recognize that *in vitro* assays are useful to screen the effects of agents on cells. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared with the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a simple extrapolation of *in vitro* assays to human therapeutic efficacy with any reasonable degree of predictability. This is especially true when the *in vitro* system used is one that artificially increases the production of a protein, perturbing the homeostasis of the transfected cell and rendering the model even further from the realities of the *in vivo* system. Furthermore, given the teachings in the specification are drawn to the effects of ZAG on melanogenesis in cancer cells Gura (Science, v278, 1997, pp.1041-1042, IDS) teaches the difficulty of extrapolating from in-vitro to in-vivo protocols in the development of therapeutics.

Additionally, as drawn to inhibiting melanin synthesis comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition, Poortmans et al (J. Lab. Clin. Med., 1968,71:807-811) teaches that ZAG is found in urine, saliva and sweat (p. 809). Poortmans et al. further teach that saliva and sweat secretions contain a high level of ZAG (p. 810). Furthermore, Lei et. al (Journal of Cellular Biochemistry, 1997, 67:216-222) teach that ZAG protein is expressed in the epidermis, p. 220 and Fig. 3. Thus, it is known that ZAG is endogneously expressed and secreted at high levels and would be expected to be present in the *in vivo* locations where melanocytes would be contacted with "therapeutic" ZAG. Given the above, in view of the known high endogenous levels of ZAG, the effects of administration of additional ZAG cannot be predicted given the apparently ubiquitous and high expression of this secreted protein. Although the specification presents *in vitro* data drawn to the inhibition of melanin synthesis, this showing clearly does not address the issue of endogenous ZAG in the *in vivo*

environment. Further, although the specification specifically teaches that, even *in vitro*, moderately to high levels of ZAG are required to achieve significant inhibition and that a threshold amount may be required, it cannot be predicted from the information in the specification whether or not this "threshold" level is already present in the in vivo environment and whether or not administration of additional ZAG would in fact have any effect whatsoever on melanin production *in vivo* as contemplated and claimed.

Additionally, although the specification teaches that ZAG was demonstrated to inhibit melanin synthesis in primary melan-A primary melanocytes in culture when ZAG was in continuous contact with the melan-A cells, once again, this *in vitro* showing does not address the issue of high levels of endogneous ZAG one of skill in the art cannot predict, for the reasons set forth above, whether addition of "therapeutic" ZAG would in fact have any effect upon melanin synthesis in vivo as contemplated and claimed.

Thus based on the data with the *in vitro* treatment of cultured cells with internally overexpressed ZAG or exogenous ZAG and the *in vivo* data with ZAG constitutively overexpressed in the B16 melanoma cells and not topically applied, no one of skill in the art would believe it more likely than not that the claimed invention would function as claimed and contemplated, that is inhibiting melanin synthesis comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition, based on the data provided.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as

originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

6. If the applicant was able to overcome the rejections set forth above, Claims 1-3 and 5-7 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting melanin synthesis in a patient comprising administering to said patient an amount of ZAG sufficient to effect said inhibition wherein said patient suffers from increased skin pigmentation, does not reasonably provide enablement for a method of inhibiting melanin synthesis in a patient comprising administering to said patient an amount of ZAG sufficient to effect said inhibition wherein said patient suffers from aberrant

skin pigmentation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting melanin synthesis comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition. The claims encompass inhibiting melanin with a sufficient amount of ZAG synthesis in a patient with any alteration of skin pigmentation.

The specification teaches that problems with increased or aberrant skin pigmentation can be psychologically devastating when widespread. Such changes may still cause significant distress even when localized to small area of the skin, especially when aberrant pigmentation involves the face and/or hands, p. 5, lines 17-20. Furthermore, the specification teaches that decreases in skin and hair pigmentation due to aging begin with decreased melanin synthesis by existing melanocytes and that ZAG concentrations in human blood increase substantially with age, p.6 lines 10-12.

The specification teaches that ZAG is produced by normal epidermal keratinocytes, where its expression increases with cellular differentiation. The specification further teaches that keratinocyte-derived factors influence melanocyte behavior, including melanocyte proliferation, dendricity, and total melanin production, p. 8, lines 5-9.

The specification teaches that ZAG decreases melanin synthesis by decreasing the amount and activity of tyrosinase in both normal and malignant melanocytes, p. 6, lines 18-21. The specification teaches that moderate to high levels of ZAG are required to achieve significant inhibition of melanin synthesis and that B16 cells are normally highly melanized despite their production of low levels of murine ZAG, para. bridging p. 7 and 8. Further the specification teaches that a threshold amount of ZAG may be required for simultaneously decreasing melanogenesis and melanin secretion, p. 8, lines 9-11. The specification teaches that B16 melanoma cells that are either transfected to strongly express ZAG or treated with exogenous ZAG have decreased melanin production *in vitro*, p. 7 lines 13-15 and Figs. 1-3. B16 tumors strongly expressing ZAG also have decreased growth and form amelanotic tumors *in vivo*, p. 7, lines 15-16. Purified ZAG, the specification teaches, also decreased melanin production by B16-V cells *in vitro*, p. 7, lines 19-20. However, the specification hypothesizes that since ZAG appears to decrease tumor cell growth and melanin synthesis *in vivo* more strongly relative to its effects *in vitro*, ZAG may also act through other indirect mechanisms *in vivo*, p. 7, lines 22-25 and Figs. 1-4.

The specification hypothesizes that the observation that ZAG-transfected tumor cells that make melanin *in vitro* are amelanotic *in vivo* demonstrates that the concentration of ZAG required to inhibit melanin synthesis is readily achieved at tumor sites *in vivo*, p. 8, lines 11-14

and Fig. 4B. Furthermore the specification teaches that ZAG similarly decreases melanin production in primary murine melanocytes *in vitro*, p. 7, lines 25-26 and Fig. 5.

One cannot extrapolate the teachings of the specification to the scope of the claims because one cannot predict without undue experimentation if ZAG will inhibit skin pigmentation in a patient that suffers from aberrant skin pigmentation. Given Merriam Webster Online Dictionary (www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=aberrant) teaches that aberrant is deviating from the usual or natural type, thus aberrant would encompass both decreases and increases in skin pigmentation. Given the specification only teaches that ZAG decreases melanin synthesis, one of skill in the art would not be able to predict the effect of ZAG in a patient that suffers from aberrant skin pigmentation wherein said aberrant skin pigmentation is decreased skin pigmentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as

contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR